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Review Article

Ethical Issues in Psychiatry Regarding Preimplantation Genetic Testing

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Abstract

Preimplantation genetic testing (PGT) is a method involving the biopsy of a fraction of an in vitro fertilized embryo, followed by the analysis of its DNA. When PGT is conducted to select embryos free of serious genetic disorders for uterine transfer, an ethical issue arises concerning the definition of "severe". Moreover, debates persist regarding the merits and drawbacks of PGT. In psychiatry, the indications for PGT primarily focus on hereditary psychiatric disorders, although many common psychiatric disorders are multifactorial in origin, marked by diverse phenotypes and courses. This complexity

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necessitates a thoughtful approach, including psychiatric support in genetic counseling provision and genetic education also linked to mental illness education. Currently, no specific laws or regulations have been established in Japan governing the application of PGT. Previously, management was based on the opinion of the Japan Society of Obstetrics and Gynecology (JSOG) and ethics committee of each medical institution. However, in 2022, the definition of "serious" expanded. For cases in which determining severity proves challenging, a collaborative approach involving: (1) reproductive medicine specialists, (2) clinical geneticists, and (3) specialists in the relevant genetic disease has been introduced. JSOG has requested cooperation from the Japanese Society of Psychiatry and Neurology to review such cases, with the society's medical ethics committee engaged in deliberation and collaboration. This paper examines ethical issues in the field of psychiatry in relation to PGT.

Keywords: preimplantation genetic testing, PGT, ethics, psychiatry, genetic disorder

Introduction

This paper examines ethical issues in the field of psychiatry surrounding preimplantation genetic testing (PGT), based on a symposium held at the 119th Annual Scientific Meeting of the Japanese Society of Psychiatry and Neurology (JSPN).

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I. Request from JSOG to JSPN for Cooperation in PGT-M Case Review

1. History of IVF and PGT

Due to recent advances in assisted reproductive technology, one in 14 children born in Japan is conceived through in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (2020),[21] and the number of pregnancies and births resulting from these techniques is increasing annually. In fiscal year 2022, general in vitro fertilization and ICSI at JSOG-certified

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assisted reproductive technology (ART) facilities became covered by health insurance, marking a shift from a specialized medical procedure, once referred to as "test-tube babies" to one of the standard forms of medical care.

The birth of the first child conceived through in vitro fertilization was reported in the United Kingdom in 1978, and in 2010, Dr. Robert Edwards, who was involved in the development of the technology, was awarded the Nobel Prize in Physiology or Medicine. Meanwhile, the first reported use of PGT was in 1990 in the UK, in a case involving sex determination for X-linked intellectual disability (X-linked intellectual developmental disorders).[3] The first IVF procedure in Japan was performed in 1983, and the first PGT procedure was conducted in 2004.

2. What is PGT?

PGT is a technique in which a biopsy is taken from a portion of an embryo undergoing in vitro culture during IVF or ICSI, and the chromosomes and genes within the cells are examined. Typically, in ICSI, a portion (approximately 5–10 cells) of the trophectoderm (TE), which is separate from the inner cell mass, which eventually develops into the fetus, is collected from a blastocyst on the 5th or 6th day of in vitro culture. The general procedure involves performing whole-genome amplification based on a small amount of genomic DNA extracted from the biopsied cells, followed by the desired genetic analysis (Figure 1).

When performed for monogenic disorders, this is referred to as PGT-M (PGT for monogenic disorders/single gene defects), and it involves testing for the presence of pathogenic variants that cause the disease. For PGT-M analysis, it is common to employ both the "direct method," which detects pathogenic variants directly, and the "indirect method," which uses linked polymorphic markers flanking the disease-causing gene to infer the presence or absence of the disease based on the segregation pattern of the pathogenic and wild-type alleles.

3. History of PGT-M introduction in Japan

The history of PGT-M in Japan began in 1998 when the Japan Society of Obstetrics and Gynecology (JSOG) published its "Opinion on Preimplantation Genetic Diagnosis,"[20] anticipating that this new medical technology would be introduced to Japan following the implementation of PGT-M in the United Kingdom in 1990. Since this statement did not clearly specify the criteria for determining which of the monogenic diseases would be appropriate for PGT-M, JSOG engaged in dialogue and consensus-

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building with patient groups for several years following the statement's release. Ultimately, in 2004, the JSOG Ethics Committee issued the first approval for cases of Duchenne muscular dystrophy. The minutes from that meeting state: "While criteria for severity may change over time, at this point, the standard of 'diseases in which symptoms severely impair daily life or threaten survival before reaching adulthood' is considered appropriate." Since then, this criterion has continued to serve as the basis for review by the Subcommittee on Preimplantation Diagnosis [currently, the Subcommittee on PGT-M for Serious Genetic Disorders within the Clinical Ethics Oversight Committee (abbreviated as the PGT-M Review Subcommittee)].

4. Convening of the ethics committee on PGT-M and revision of the opinion

Since the initial opinion was issued in 1998, individual reviews have been conducted on a case-by-case basis rather than by disease category, with the aforementioned "severity criteria" in mind. However, in 2018, a new application was received from a couple with retinoblastoma that did not meet the conventional severity criteria. This raised the question of whether to continue applying the traditional criteria in the future. In response, JSOG led the convening of the PGT-M Ethics Deliberative Council from 2020 to 2021. The committee solicited opinions from experts in various fields and the general public (public comments) and held three rounds of discussions.[22] A variety of opinions were received, and ultimately, a consensus was reached that the criteria for determining the "severity" of a disease, which had been considered appropriate in 2004, needed to be adapted to reflect current times. Thus, regarding cases that had previously been "disapproved," such as those involving "diseases that do not result in death or a bedridden status by the age of 20," for example, PGT-M in families with hereditary tumors that may develop in adulthood, such cases would no longer be uniformly rejected, but instead would be reconsidered individually on a case-by-case basis. Consequently, the "Opinion on Preimplantation Diagnosis" was ultimately revised and published in January 2022 as two separate documents: the "Opinion on Preimplantation Genetic Testing for Serious Genetic Disorders" and "Opinion on Preimplantation Genetic Testing for Infertility and Recurrent Miscarriage." The definition of "severity" was also explicitly provided within the "Opinion on Preimplantation Genetic Testing for Serious Genetic Disorders," as follows: "In principle, a condition in which symptoms that severely impair

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daily life appear before reaching adulthood, or a situation arises where survival is at risk, and for which there is currently no effective treatment to prevent it, or which requires highly advanced and invasive treatment." Currently, PGT-M is being performed clinically in accordance with this new opinion and supplementary rules.[23)]

5. Request for review cooperation regarding PGT-M to JSPN

In conjunction with the revision to the aforementioned new opinion, regarding applications for new cases that do not meet the conventional criteria for severity, if the PGT-M Review Subcommittee fails to reach a unanimous agreement, a higher-level body, the PGT-M Clinical Ethics Individual Review Committee, will be convened, and the policy is to conduct a comprehensive review that incorporates not only the medical judgments previously made by the PGT-M Review Subcommittee but also considerations of the applicant couple's life circumstances and their specific situation.[23)]

Furthermore, in response to external criticism raised at the aforementioned Ethics Council meeting, which pointed out that the physicians who submit PGT-M case applications (reproductive medicine specialists and clinical geneticists whose primary field is obstetrics and gynecology) and the PGT-M Review Subcommittee are primarily composed of obstetricians and gynecologists, potentially leading to bias in determining indications and compromising neutrality in both medical and societal contexts, it was decided to incorporate, into the case application and review process: i) the opinions of physicians (individual specialists), and ii) written opinions from "specialized academic societies involved in the diagnosis and treatment of each genetic disorder."[24)]

Based on the above, under the "Request from JSOG to JSPN for Cooperation in PGT-M Case Review," the following cooperation was requested: i) in cases where a couple from a family with a genetic disorder primarily characterized by neuropsychiatric symptoms requests PGT-M, the attending physician (a psychiatrist) is requested to prepare an application form stating how they assess the appropriateness of PGT-M for that family (using the JSOG prescribed format: "Consent Form M3"), and ii) JSPN is requested to prepare a written opinion stating its judgment regarding the implementation of PGT-M for genetic disorders primarily characterized by neuropsychiatric symptoms in that specific family (using the prescribed format "Form: Opinion A") (Figure 2).

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6. Summary

Since PGT-M is a medical procedure based on IVF, JSOG has up until now taken the lead in formulating opinions and exercised self-regulation through professional autonomy. However, despite the PGT-M Review Subcommittee's decision to "disapprove" the procedure following careful review, there are still couples who wish to undergo PGT-M and choose to have it performed overseas or at non-accredited facilities. Furthermore, the "opinion" issued by JSOG, a professional association, has no legal binding force, and there are also criticisms pointing out whether it is possible to make truly neutral judgments amidst today's diverse values. Although JSOG is striving to regulate implementation as the most feasible approach under the current circumstances, there are limitations to this approach, and JSOG has requested the government to establish a "public platform responsible for deliberation, governance, and oversight of bioethical issues."

II. Challenges in the Field of Psychiatry Regarding PGT

1. Background of challenges in the field of psychiatry regarding PGT—relationship with the (former) Eugenics Protection Law—

The author (N.O.) has, in the course of daily psychiatric practice, heard concerns from patients and their families, such as: "My psychiatric disorder was inherited from my parents, so perhaps it will never get better," or "My parents were first cousins, so perhaps that is why my son developed a psychiatric disorder." Faced with psychiatric disorders that can affect the lives, futures, and even the very survival of patients and their families, the author (N.O.) felt compelled to respond, even in a small way, to their anguish, which stems from an inability to avoid seeking some cause for their condition. Consequently, the author (N.O.) re-studied genetics and has been providing genetic counseling.[27)]

While administering genetic counseling for psychiatric disorders, the author felt that the (former) Eugenics Protection Law, which existed in Japan from 1948 to 1996, had influenced the perspectives of individuals with psychiatric disorders and their families regarding genetics. The appendix to Article 4 of this law listed schizophrenia, bipolar disorder, epilepsy, and intellectual developmental disorders under "hereditary mental illness and hereditary intellectual developmental disorders," and eugenic surgeries (compulsory sterilization) were performed without the individual's consent. However, there is absolutely no medical basis for the term "hereditary," which appears to have been based on

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the assumption of Mendelian inheritance.

Although the term "hereditary mental disorders and hereditary intellectual developmental disorders" was eliminated with the enactment of the Maternal Health Act, a general understanding of the relationship between psychiatric disorders and heredity has not yet become sufficiently widespread. Given this, the challenges in the field of psychiatry surrounding PGT must be examined not only in relation to psychiatric disorders associated with genetic disorders, but also in relation to psychiatric disorders that are multifactorial in nature.

2. Psychiatric disorders associated with genetic disorders

The scope of PGT-M, which is the focus of this paper, is limited to cases where "both or either of the couple seeking this procedure are carriers of a genetic mutation or chromosomal abnormality that could result in the birth of a child with a severe genetic disorder."[23] Therefore, we will review psychiatric disorders associated with genetic disorders for which causative genomic variants have been identified.

Among genetic disorders with identified causative variants, conditions such as 22q11.2 deletion syndrome, 3q29 deletion syndrome, neurofibromatosis, tuberous sclerosis, and Rett syndrome affect multiple organs, including the brain, and are associated with a high rate of comorbid psychiatric disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder, and schizophrenia, from child- through to adulthood.[16] In the majority of these cases, the causative variants are de novo (not inherited from parent to child). Therefore, although these conditions are classified as genetic disorders, they differ from 'hereditary' disorders in the narrow sense of a variant transmitted from parent to child; this distinction needs to be explained during genetic counseling.

A characteristic of these genetic disorders that can cause psychiatric disorders is the phenotypic variability (heterogeneity) observed among patients with the same variant; even within the same family, phenotypes (both psychiatric and physical) are diverse, and the relationship between the geno- and phenotype is not one-to-one. Thus, while patients with these variants have a higher incidence of psychiatric disorders compared with the general population, the incidence rate is not 100%, and the specific psychiatric disorder that develops varies from patient to patient. Furthermore, the severity varies; for example, the degree of intellectual disability exhibited by

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patients with 22q11.2 deletion syndrome varies widely.

Confirming a diagnosis through genetic testing enables medical care that accounts for the presence of multi-organ disorders, as well as the early diagnosis and appropriate management of potential psychiatric disorders. However, genetic counseling that takes into account phenotypic diversity requires more than just providing general information; it demands an understanding of the specific characteristics and needs of individual patients and their families, and the provision of information and support based on that understanding.[11] Therefore, it is important to engage in two-way communication between healthcare providers and patients and their families, and provide appropriate information and support tailored to their respective cognitive abilities and living environments.

Under the (former) Eugenics Protection Law, patients with genetic disorders, including tuberous sclerosis, were subject to compulsory sterilization. However, i) de novo variants, which differ from the concept of "heredity" as "transmitted from parent to child" as understood during the era of the (former) Eugenics Protection Law, are also involved in the onset of psychiatric disorders. ii) Even among individuals with the same variant, the possible clinical presentations are extremely diverse. Furthermore, iii) individuals with a given variant may present with diverse clinical manifestations depending on their developmental stage or age; thus, the opinion that "clinical manifestations are determined by genetics" is not valid. Consequently, the fundamental concept of the (former) Eugenics Protection Law, that "a child's psychiatric disorders can be predicted with 100% certainty based solely on the parent's genomic information (regardless of whether it is passed from parent to child)," has been refuted.

Based on the above points, we will examine PGT for psychiatric disorders associated with genetic disorders, while considering the situation overseas.

3. PGT for psychiatric disorders associated with genetic disorders

When discussing future reproductive options with patients who have reached adulthood, genetic counseling that takes into account each individual's characteristics is essential. The National Health Service (NHS) website, "Health Education England," includes information on genetic counseling for 22q11.2 deletion syndrome.[15] It recommends that families with this syndrome confirm the presence or absence of the relevant variant and use this information for health management; furthermore, it

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encourages patients to consider reproductive options such as prenatal diagnosis and PGT. Note that in the UK, genetic testing is covered by the NHS. Furthermore, the website of the Human Fertilization & Embryology Authority (HFEA), operated by the UK government,[6] lists conditions eligible for PGT-M, including neurofibromatosis, tuberous sclerosis, and Rett syndrome.

A study involving 13 patients with 22q11.2 deletion syndrome in the UK reported on how individuals perceive reproductive choices based on genetic testing.[13] The results showed that patients with this syndrome, when they did not wish to have a child with the condition based on genetic testing, tended to choose PGT-M over prenatal testing that results in fetal termination, a trend similar to that observed for other genetic disorders (such as myotonic dystrophy and retinitis pigmentosa). Conversely, some patients with 22q11.2 deletion syndrome viewed the disease characteristics associated with their condition as an integral part of their identity, and indicated a preference against embryo selection based on genetic testing.

Decisions regarding PGT-M are complex and influenced by the medical, welfare, and social circumstances surrounding the patient and family, as well as the patient's own medical history and personal views. Looking at the situation in Japan, for example, noninvasive prenatal genetic testing (NIPT) using maternal blood, which includes assessing whether a fetus carries disease-causing variants such as the 22q11.2 deletion, can be easily performed simply by drawing blood from the pregnant woman. Consequently, there are cases where it is performed too readily without adequate genetic counseling. However, various psychiatric disorders for which causative variants have been identified often present with symptoms affecting multiple organs; therefore, to provide clinical care that takes into account the relationship between organs and disease, an interdisciplinary network equipped with a genetic counseling system capable of coordinating between departments is essential.[26] Nevertheless, the current reality in Japan is that medical institutions possessing such network capabilities are extremely scarce.

4. PGT for multifactorial diseases, including psychiatric disorders

While causative variants for genetic disorders are rare in the general population, some variants are relatively common. Genome-wide association studies (GWAS) are conducted to investigate associations with multifactorial diseases using single base substitutions that are common

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across the entire genome. In recent years, the polygenic risk score (PRS), calculated by combining numerous SNPs, has been proposed, and PRSs to assess the risk of multifactorial diseases, including psychiatric disorders, are being reported one after another. Several overseas companies have launched PGT-polygenic (PGT-P) services based on PRSs for multifactorial diseases derived from GWAS. The conditions for which PGT-P scores are calculated include: diabetes, coronary artery disease, malignant tumors, and schizophrenia. However, from a genetic statistical perspective, the implementation of these tests is not yet considered appropriate, and there are concerns that they could lead to eugenic ideologies involving the exclusion of individuals deemed unsuitable for society.[43)]

5. Toward improving genetic literacy—linking with education on psychiatric disorders—

In Japan, education on human genetics in primary and secondary schools remains overwhelmingly insufficient compared not only with developed nations but also many other countries.[8)] In particular, the public's knowledge regarding the "potential for diversity" in traits determined by multifactorial inheritance, including psychiatric disorders, and genetic information is extremely limited. For a long time, until education on psychiatric disorders began in high schools in April 2022, misunderstandings and prejudices regarding psychiatric disorders arose due to a lack of knowledge and insufficient literacy stemming from this educational deficit; the same applies to the taboo surrounding genetics and discriminatory attitudes. Therefore, it is necessary to fundamentally re-examine and reconstruct educational policies regarding human genetics, and advance initiatives to improve genetic literacy. Enhancing genetic education in conjunction with education on psychiatric disorders will not only help ensure the appropriate dissemination and development of genetic and genomic medicine, including PGT-M, among the public, but is also indispensable for preventing unjust discrimination based on genetic information and resolving the misunderstandings and prejudices regarding psychiatric disorders that still persist due to the legacy of the (former) Eugenics Protection Law.

6. Summary

When considering the challenges of PGT in the field of psychiatry, it is necessary to expand the medical and welfare systems for psychiatric disorders associated with the aforementioned genetic disorders, as

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well as the systems capable of providing genetic counseling for patients and families concerned about psychiatric disorders and genetics more broadly. This requires the development of necessary human resources and enhancement of genetic education in conjunction with education on psychiatric disorders.

III. Genetic Clinics for the Adolescent and Young Adult (AYA) Generation: Clients' Conflicts Regarding PGT and the Role of Psychiatric Care

1. What is genetic counseling?

Genetic testing, in addition to diagnosing manifested genetic disorders can also estimate the risk that future offspring may inherit susceptibility to, or eventually develop, the disease. Consequently, it can cause clients (patients and their families) to experience anxiety and distress distinct from those associated with other medical tests. Genetic counseling is defined by the National Society of Genetic Counselors (NSGC) as: "a process that helps people understand and adapt to the medical, psychological, and familial impacts of the genetic factors underlying a disease."[32] Thus, it involves providing a genetic interpretation of the disease and offering clients information on inheritance patterns, genetic testing, treatments, preventive measures, social resources, and research, thereby supporting them in making informed choices. However, support, advice, psychological counseling, and psychotherapy aimed at alleviating the psychological, social, and spiritual distress experienced by clients undergoing genetic counseling are conceptually distinct from genetic counseling itself. We believe that the role of psychiatric professionals in genetic medicine warrants further discussion and re-examination.

2. Conflicts in genetic counseling

In genetic counseling related to reproductive medicine, information is provided regarding future predictions, including potential outcomes for the child before conception or birth, as well as welfare services. Issues anticipated to involve psychiatrists in reproductive medicine include: i) anxiety regarding whether common psychiatric disorders, which are multifactorial, will be inherited by the next generation, and ii) the nature of medical and other support for the psychiatric symptoms of individuals with genetic disorders. Here, we focus mainly on point ii, namely psychiatric symptoms associated with relatively common chromosomal disorders, while briefly discussing point i. Currently, genetic counseling for multifactorial psychiatric disorders, such as schizophrenia and mood

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disorders (point i), primarily utilizes findings from family studies; however, the clinical application of PRS based on findings from genomic analysis is anticipated in the future. In the Japanese population, the accumulation of disease-related genomic data is still insufficient. Furthermore, due to the inherent ambiguity of genomic characteristics, while PRS is used for risk prediction, its clinical application as a diagnostic method is still considered difficult. Therefore, prenatal or preimplantation genetic testing for psychiatric disorders based on PRS is not currently performed in Japan.

3. The struggles of patients with genetic disorders in the AYA generation

In clinical genetic practice, an increasing number of patients and families seek psychiatric support in addition to genetic counseling.

As reported,[31] the life expectancy for individuals with Down syndrome has improved from less than 10 years 50 years ago to the 60s today. With the advancement of pediatric surgical techniques, such as cardiac surgery, the number of clients in the Adolescent and Young Adult (AYA) generation living with genetic or chromosomal disorders has increased. In relatively common chromosomal disorders such as Down syndrome, 22q11.2 deletion syndrome, and Williams syndrome, it is not uncommon for patients to develop neurodevelopmental disorders, including intellectual disabilities, in addition to physical symptoms.[34] Furthermore, it is well known that patients with congenital heart disease are prone to developing anxiety disorders as a secondary condition. While patients with severe neurodevelopmental disorders continue to receive support and care in facilities such as nursing homes even after reaching adulthood, those with relatively mild neurodevelopmental disorders are often excluded from pediatric medical care once they reach the AYA generation. They are then expected to adapt to society through programs such as employment for people with disabilities, employment support service providers, or vocational support centers. This increases the risk of developing psychiatric symptoms, such as adjustment disorders and acute regression syndrome, which may be triggered at least in part by psychosocial stress. It is desirable for psychiatric professionals to provide support for both the individual and their parents by conducting medium- to long-term follow-up across the life stages from school age through the AYA generation and by appropriately assessing psychiatric symptoms.[1]

Furthermore, as patients enter the AYA generation, they experience age-

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appropriate developments in independence and physical maturity, and often begin to desire a partner. In genetic counseling, practitioners frequently receive urgent consultations from parents regarding the reproductive health of affected individuals, alongside the affected individuals with chromosomal or genetic disorders themselves. Some chromosomal disorders, such as 22q11.2 deletion syndrome and Williams syndrome, are inherited in an autosomal dominant manner and carry a 50% risk of transmission to offspring, whereas Down syndrome is usually sporadic. Parents love their children and have supported their growth through immense hardship; however, they are acutely aware that even after physical symptoms are cured, many patients have limited daily living abilities, including parenting, due to conditions such as neurodevelopmental disorders. Therefore, it is not surprising that parents, perhaps even more so than the patients themselves, hope that the condition will not be passed on to a child when AYA-generation patients seek intimate relationships or wish to have children with a partner.

4. Issues with NIPT and PGT

In Japan, NIPT, which detects the risk of fetal chromosomal abnormalities and congenital disorders through maternal blood testing, is performed. Facilities certified by the Japanese Association of Medical Sciences are required to screen for trisomies of chromosomes 13, 18, and 21 (and are not permitted to report on other items, including sex).[19] However, since the latest testing technologies can detect not only quantitative abnormalities of a single chromosome but also partial deletions of relatively small chromosomal regions,[34] there are instances where NIPT performed overseas or at non-accredited facilities reports the possibility of 22q11.2 deletion syndrome. Since NIPT is a non-diagnostic test, if a chromosomal abnormality is suggested, a more invasive amniocentesis must be performed on the mother or fetus to confirm the diagnosis; consequently, some clients wish to use PGT-M to avoid transmitting the disorder to future offspring. Conversely, regarding PGT, particularly PGT-M, which analyzes the genes and chromosomes of embryos and is currently under discussion by the Japan Society of Obstetrics and Gynecology (JSOG), there are strong calls for cautious implementation and regulation, given concerns that reproductive selection based on genomic information may evoke ethical concerns related to eugenics.[25] Debate is likely to continue regarding whether chromosomal partial deletion

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syndromes, such as 22q11.2 deletion syndrome, for which life expectancy has improved substantially, should be indications for PGT-M. From the clients' perspective, there is frustration with the current state of domestic healthcare, where testing is available overseas and at some non-accredited facilities, yet cannot be performed at accredited facilities that provide genetic counseling.

5. Genetic medicine and the four principles of medical ethics

The characteristics of genetic information include: "immutability" (it does not change over a lifetime), "predictability" (regarding future onset), "sharedness" (within blood relatives), and "ambiguity" (genetic information alone cannot determine whether a condition will develop, or the age at onset or severity). PGT-M determines predictability regarding the child based on sharedness, but at the same time, its ambiguity is a subject of debate. When prenatal genetic testing is evaluated against the four principles of medical ethics (respect for autonomy, non-maleficence, beneficence, and justice), a conflict arises between the principle of respect for autonomy for the client (the affected individual and their parents) and concern for the welfare of the future child. Furthermore, even if the affected individual wishes to give birth (respect for autonomy), the affected individual's parents may express concerns about the disadvantages associated with childbirth, such as: "I don't want my daughter to go through the same hardships by giving birth to and raising a child with the same disease," or "I don't want her to feel guilty for passing the disease on to the child." In such cases, the principle of respect for autonomy and principle of beneficence may also conflict. Due to these concerns, many parents oppose their daughter's marriage or having children. In prenatal genetic testing, including PGT-M, it is inevitable that parents of affected individuals with psychiatric symptoms would wish for their daughter to have a healthy child to prevent major disruptions to her life; therefore, it is difficult to dismiss such concerns simply as manifestations of eugenic ideology when providing genetic counseling.

6. Summary

Psychiatric professionals should establish early intervention and support systems for those with neurodevelopmental disorders and other conditions to address the psychological, social, and economic distress of clients in the context of genetic medicine. Furthermore, psychiatric professionals should engage more actively in discussions regarding

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the indications for genetic testing, including PGT-M, not only for psychiatric disorders but also for genetic disorders accompanied by psychiatric manifestations.

IV. Trends in Medical Ethics Committees Related to PGT-M

1. Origin of the discussion regarding Opinion Paper A on PGT-M

JSPN was requested to set up a system to prepare Opinion Paper A on PGT-M on August 3, 2021, while JSOG was conducting preliminary consultations regarding changes to the criteria for determining "severe" conditions in PGT-M. At JSPN, under the direction of the president, the Medical Ethics Committee started to formulate a policy to deal with this issue. Recognizing that the issue involved broad and complex ethical challenges, JSPN determined that sufficient time for deliberation was necessary and replied to JSOG on October 5, 2021, requesting that response be deferred.

2. Deliberation process in the Medical Ethics Committee

To deepen understanding of this issue and establish a policy to deal with, the Medical Ethics Committee held three internal study sessions between November 2021 and March 2022. In organizing these sessions, the Committee took care to incorporate a wide range of perspectives regarding the application of genomic technology in the field of reproductive medicine, including: (i) opinions from a cautious standpoint, (ii) opinions from a proactive standpoint, and (iii) opinions from the standpoint of responsible review board.

1) Opinions from a cautious standpoint

Around 1997–1998, when JSOG first defined the scope of PGT-M as limited to severe genetic disorders, countries around the world uniformly took a cautious stance regarding the application of genomic technology to reproductive medicine. Today, however, the United States, United Kingdom, and China are particularly proactive in applying this technology and leading the world in this field. The cost of genetic analysis has fallen markedly over the past 20 years, making it readily accessible even to clinics and creating a market for these services. There is also concern that the commercial aspect of genetic analysis may fuel anxiety among those involved. Regarding PGT, which has traditionally been conducted under JSOG review "while it was limited to applications for severe genetic disorders, the definition of "severe" remains ambiguous. Even overseas, there is a view that "serious genetic diseases" should be the target of PGT, but debates have arisen because it is unclear exactly which diseases "serious"

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and "very serious" refer to,[10] and such criticisms have been raised by some obstetricians and gynecologists. There are many technologies closely related to PGT-M, such as preimplantation genetic testing for aneuploidy (PGT-A), preimplantation genetic testing for structural rearrangements (PGT-SR), and even human genome editing, and these involve even more serious ethical challenges. Therefore, when discussing these issues, it is necessary to fully consider the risk of the moral hazard known as the "slippery slope."[9]

2) Opinions from a proactive standpoint

Guest lecturer shared opinions advocating for more active use of PGT-M were introduced,[30] such as "Healthcare providers should present us options and support the process by which patients make their choices" and "We hope for consideration of the perspectives and feelings of women who wish to use PGT-M rather than prenatal diagnosis that may involve abortion". The lecturer also noted that there is a shortage of psychiatric professionals in the field of genomic medicine, and a lack of medical resources sufficient to adequately accommodate the wishes of those seeking more active use of PGT-M. It was also pointed out that, when discussing the clinical application of PGT-M, there is no underlying legislation, resulting in a situation where JSOG must make decisions on significant matters that involve ethical and social challenges.

3) Opinions from a standpoint of responsible review board

JSOG has served as the contact point for applications regarding research using PGT-M, carefully reviewing and deciding on approval or disapproval of implementation, and seeking opinions from specialists in other medical departments when necessary. This framework for reviewing PGT-M indications had remained unchanged for over 20 years since 1998; however, the opinions of individuals wishing to actively utilize reproductive technologies have diversified, leading to a growing discrepancy with the needs of present-day society. In connection with the aforementioned revision of the definition of "severity" and related matters conducted in January 2022,[25] JSOG requested that relevant academic societies recommend experts who could provide written opinions when new applicants emerge who wish to pursue PGT-M indications but do not meet the traditional criteria for "severity." JSOG also suggested to establish a working group, regarding individual case applications, with the following request: "We would greatly appreciate it if you could prepare a written opinion on behalf of JSPN. In order to achieve harmony between the views of those seeking the active use of PGT-M and

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society at large, we ask that this issue be discussed across many academic societies and that those societies actively engage with it."

4) Discussions in the Medical Ethics Committee

Despite many differing opinions among the three positions above, there was agreement that the lack of domestic laws serving as a foundation for discussing this issue further complicates the matter. Even considering of the lack of domestic laws on PGT-M, the opinions of the proactive side have a clear legal basis in reproductive health rights, whereas the opinions of the cautious side lacked clear legal logic; therefore, it was deemed inappropriate for JSPN to refuse cooperation on this request from JSOG. The possibility that applications might be made on the basis of eugenic thinking, discriminatory views, or ideas rooted in misconceptions about genetics was also discussed, and it was confirmed that sufficient individual attention would be paid to each of these possibilities when drafting Opinion Paper A.

3. Policy on Opinion Paper A on PGT-M

Ultimately, it was concluded that JSPN would cooperate with the review process through the preparation of Opinion Paper A on PGT-M, subject to several conditions, including that JSOG would regularly provide JSPN with information regarding PGT-M for severe genetic disorders. The conclusion reached by the Medical Ethics Committee was communicated to the Board of Directors, and following the Board's decision, the response policy was communicated to JSOG (dated May 21, 2022). Furthermore, the "Working Group on Preimplantation Genetic Testing" was established to continuously gather diverse opinions and academic insights regarding ethical issues in this field, examine the inherent ethical challenges, and prepare to take necessary actions when a request for the Opinion Papers arise.

V. Recent Ethical Issues Surrounding PGT

In bioethics, classic issues related to assisted reproductive technologies, such as the moral status of embryos and eugenics, have been debated for over half a century. Here, focusing primarily on insights from the English-speaking world where such discussions have been conducted ahead of other regions, this paper organizes the ethical issues related to PGT that have accumulated over the past quarter-century and shares an awareness of the complexity of this problem.

1. Who should make decisions regarding PGT?

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Based on the principle of respect for autonomy and reproductive rights, the final decision to undergo PGT should be made based on the voluntary consent of both partners. However, even if a couple wishes to undergo PGT, there may be cases where they are in an abusive relationship involving reproductive coercion, or where there are issues regarding their ability to raise a child. Furthermore, in cases where there is a high risk of disability but one partner does not wish to undergo PGT, the issue of decision-making capacity may arise. Nevertheless, many commentators take the view that reproductive autonomy should take precedence even in such cases.

2. What should PGT be used for?

PGT is currently being considered with the aim of reducing the disease burden on children. While many guidelines state that enhancement targeting culture-dependent traits is not permissible,[41] some take the view that mental health-related characteristics, such as temperament, intelligence, and risk-taking propensity, are linked to well-being, and that advances in PGT technology may enable intervention in these areas.[37]

Furthermore, the issue of reverse selection, selecting embryos that would result in children possessing traits believed to reduce well-being, also arises.[42] Opinions are divided on whether facilities are permitted to refuse PGT requests made for the purpose of reverse selection. How reverse selection is handled becomes crucial when addressing eugenic critiques of PGT and respecting reproductive autonomy, particularly from the perspective of maintaining consistency in normative discussions regarding reproductive medicine, including abortion.

As a related normative argument, there is the "person-affecting view," which emphasizes that, unlike vaccinations, PGT alters the embryo that will develop into a child and is therefore not an intervention on the same individual. However, if the person-affecting view is accepted, the following example would also be permitted: "A woman is currently suffering from rubella. If she becomes pregnant now, she will likely give birth to a child who is blind and deaf. If she waits three months, this will not happen. However, she thinks, "Even if I become pregnant now, that child will not be the same (genetically speaking) as the child I would conceive three months from now. Therefore, even if the child conceived now were to be blind and deaf, it would be a different child from the one that would have been conceived three months later; thus, conceiving now does not harm the child in any way."[37] D.

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Parfit, considering such cases, suggests the possibility of focusing impersonally on the quality of experience from a perspective that transcends individual persons, rather than on the identity of the person.[28] Furthermore, a 2002 report by a World Health Organization (WHO) advisory committee on PGT[45] has also been published, which argues that PGT itself should be considered separately from discrimination against people with disabilities who are currently alive. Similarly, it has been pointed out that existing social attitudes and stigma toward disability may influence the use of PGT,[2][17] and research based on empirical bioethics regarding changes in stigma before and after the introduction of PGT will be important.

3. What are the purposes of PGT?

There are three main perspectives regarding the purposes of PGT. First, there is the position aimed at alleviating the anxiety of parents who themselves have disabilities and promoting reproductive autonomy; this effect has been verified through prenatal testing.[39] From a virtue ethics perspective, some commentators take the view that it is permissible for parents who possess the "virtue of loving care," that is, who sincerely wish for and consider the child's well-being, to undergo PGT.[7] Second, there is the position that considers the well-being of the unborn child. And third, there is the position that considers the well-being of the parents.

Regarding the second position, the principle of procreative beneficence is a noteworthy topic. While Sandel, M.J. argued that there is no specific obligation regarding the selection of children,[35] Savulescu, J. and others argued that the principle of procreative beneficence does exist. This is the idea that "if a couple decides to have a child and has the option to choose, they have a strong moral reason to select, from among the children they could have, the one whose life is expected to be better than any other child's, or at least no worse, in light of relevant available information."[37][38] Savulescu et al. explain that this principle does not permit coercion but rather signifies a level of justification for persuasion; conversely, some commentators view it as a supererogatory obligation[36] or simply as a rational act.[5] As a critique of the principle of procreative beneficence, and just as the severity criteria for PGT are composed of diverse perspectives, including medical, psychological, and social ones,[14] some point to the technical difficulties of predicting the quality of life (QOL) and difficulty of defining the "best life."[4][29] However, there are counterarguments[5] stating that technical difficulties do not

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constitute grounds for rejecting ethical claims, as well as positions[29] that acknowledge the need for certain boundaries.

4. When should information regarding PGT be provided and decisions made?

In routine clinical practice by non-genetic specialists, whether there is a duty to disclose PGT technology, and the timing of disclosing related information present challenges. Since similar wrongful birth lawsuits have been observed in Japan, it is considered necessary to engage in discussions involving legal experts in the future. However, it is not viewed as desirable to disclose genetic possibilities indiscriminately. If the patient hopes to have children in the future, it is considered necessary to address this possibility as part of life course support, while providing psychological support during outpatient visits and collaborating with genetic specialists when necessary.

5. How should the PGT decision-making process be conducted?

For couples beginning to consider PGT, genetic counseling is central to the decision-making process, and opportunities for such counseling must be ensured. The ethical themes in genetic counseling are considered to be the couple's autonomy and child's well-being. In this context, from the perspective of relational autonomy, attention should be paid to the potential for influence by others and possibility of internalizing social prejudice or oppression.[12] Furthermore, regarding the child's well-being, it is important to clearly illustrate the actual living situations of people with the target conditions based on specific case examples.[33]

It should be noted that some viewpoints define reproductive autonomy as that in the sense of not being coerced by anyone, rather than as autonomy that demands a high degree of rationality. If a couple can demonstrate the benefits for the couple's or child's well-being, it is considered that diversity in participation (undergoing testing or not), diversity in decision-making methods (expressing clear intent, providing a rationale that is reasonable to healthcare providers, or not), and diversity in the content of decisions (giving birth to a child with or without a disability, or not) should be guaranteed. While maintaining a critical stance toward coercion, condemnation, prejudice, and discrimination against couples, it is likely that flexible and long-term support, providing psychological and social support regardless of the choice the couple makes, will be necessary.

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6. Section summary

This section has outlined the major ethical issues related to PGT, but the ethical challenges of PGT are not limited to these. Furthermore, there are issues where other fields may offer more useful approaches, such as how to implement PGT systems, whether support for people with disabilities and their families, normalization, and empowerment are sufficient, and how to ensure quality of care and address budget allocation issues[44] if specific diseases decrease due to PGT. PGT is of a trans-science nature, and in addition to normative discussions, collaborative analysis with other academic disciplines, such as the philosophy of science, law, sociology, political science, and sociology of science and technology, as well as open discussions involving those directly affected and other parties concerned are indispensable and will continue to be required.

Conclusion

In June 2023, the Genome Medicine Promotion Act (formally: Act on the Comprehensive and Systematic Promotion of Measures to Ensure that Citizens Can Receive High-Quality and Appropriate Genomic Medicine with Peace of Mind) was enacted, and measures to ensure that the public can receive high-quality and appropriate genomic medicine with peace of mind were to be promoted in a comprehensive and systematic manner. The Genome Medicine Promotion Act calls for the realization of high-quality genomic medicine across a wide range of medical fields, including psychiatry, so that the general public can widely benefit from it, while also stipulating that appropriate consideration must be given to bioethics and that no unjust discrimination may occur. Furthermore, it explicitly states that the national government has a duty to formulate and implement genome medicine policies in a comprehensive and planned manner in accordance with these basic principles.[40]

PGT, which is the subject of this paper, is a medical technology that utilizes genetic diagnostic technology, which is a form of genomic medicine. Given that the Genome Medicine Promotion Act clearly stipulates the government's responsibilities, a basic legal framework should be established for PGT as well, and a platform jointly established by academia and society with public support should be set up. To this end, it is necessary to establish a public agency responsible for reviewing reproductive medicine, including PGT, and bioethics; it is expected that this agency will broadly deliberate on and reach consensus regarding the principles of

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bioethics and advance the establishment of norms.[18)]

Due to recent advances in reproductive medicine, it has become impossible to avoid issues related to PGT even in the field of psychiatry. It is necessary to learn about prenatal and preimplantation genetic testing and deepen our understanding of the ethical issues involved.

This article was prepared based on the Committee Symposium (Medical Ethics Committee) “Ethical Issues Surrounding Pre-implantation Genetic Testing: From a Psychiatric Perspective” held at the 119th JSPN Annual Meeting.

Conflict of Interest

Norio Ozaki has the following conflicts of interest (COI) with the following companies: patents and royalties, Takeda Pharmaceutical Company Limited and Mitsubishi Tanabe Pharma Corporation; honoraria for lectures, Otsuka Pharmaceutical Co., Ltd., Sumitomo Pharma Co., Ltd., Viatris Pharmaceuticals Japan Inc., Eisai Co., Ltd., EA Pharma Co., Ltd., and Takeda Pharmaceutical Company Limited; research funding/grants, The KAITEKI Institute, Inc., Ricoh Company, Ltd., Sumitomo Pharma Co., Ltd., Eisai Co., Ltd., Takeda Pharmaceutical Company Limited, and Otsuka Pharmaceutical Co., Ltd.; scholarship donations, The KAITEKI Institute, Inc., Otsuka Pharmaceutical Co., Ltd., Sumitomo Pharma Co., Ltd., Eisai Co., Ltd., and Mitsubishi Tanabe Pharma Corporation; other advisory fees, etc., Sumitomo Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and Mochida Pharmaceutical Co., Ltd.

The other authors have no conflicts of interest to disclose.

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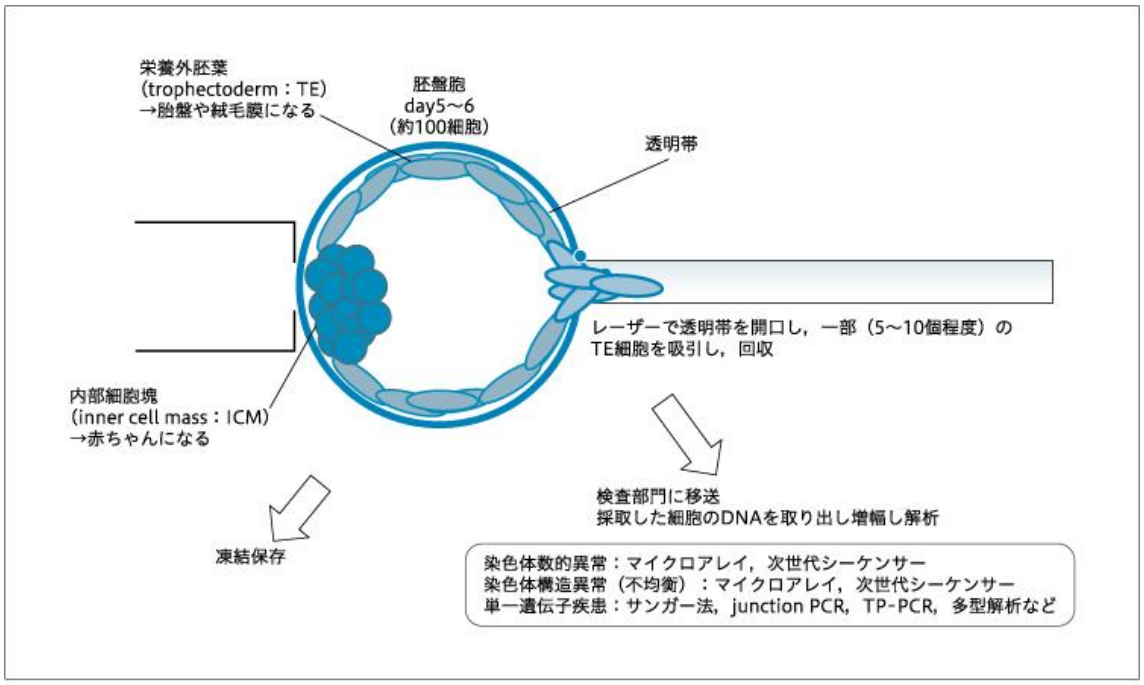

図 1　着床前遺伝学的検査（PGT）とは

Figure 1: What is preimplantation genetic testing (PGT)?

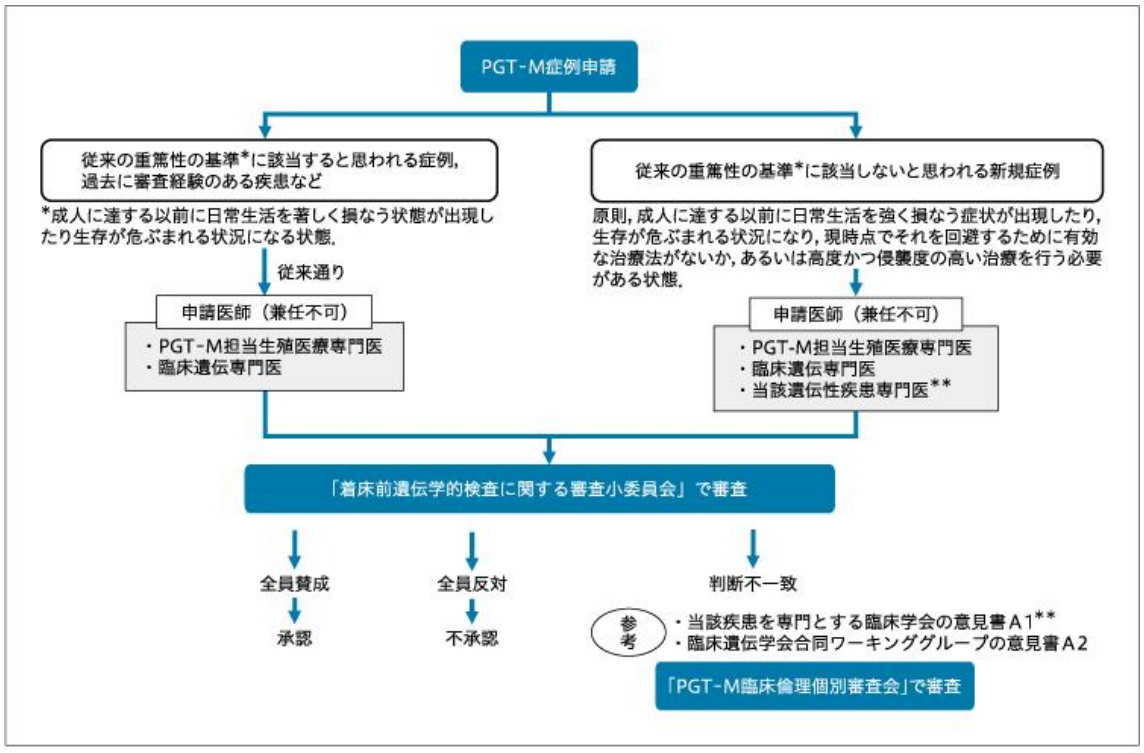

図 2　PGT-M 実施の審査過程

**日本精神神経学会への依頼事項.

Figure 2: Review process for PGT-M implementation

**Requests for JSPN.

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